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Cuijpers, Pim; Ebert, D.D.; Acarturk, C.; Andersson, G.; Cristea, I.A.

published in
Behavior Therapy
2016

DOI (link to publisher)
10.1016/j.beth.2016.04.007

document version
Publisher's PDF, also known as Version of record

Available online at www.sciencedirect.com

ScienceDirect

Behavior Therapy 47 (2016) 966–980

Behavior Therapy

www.elsevier.com/locate/bt

Personalized Psychotherapy for Adult Depression: A Meta-Analytic Review

Pim Cuijpers

VU University Amsterdam, EMGO Institute for Health and Care Research, and Innovation Incubator

David D. Ebert

Innovation Incubator and Friedrich-Alexander University Erlangen-Nüremberg

Ceren Acarturk

Istanbul Sehir University

Gerhard Andersson

Linköping University and Karolinska Institutet

Ioana A. Cristea

Babes-Bolyai University and University of Pisa

Personalized medicine is aimed at identifying which characteristics of an individual predict the outcome of a specific treatment, in order to get a better match between the individual and the treatment received. We conducted a systematic review and meta-analysis of randomized trials comparing two psychotherapies directly in a group of depressed patients with a specific characteristic. We focused on the six most examined types of psychotherapy for adult depression. Our searches resulted in 41 studies with 2,741 patients who met inclusion criteria. These 41 studies examined 27 specific characteristics of patients. Power calculations indicated that we would need 4 studies for each characteristic to find a clinically relevant effect size set at $g = 0.50$ and 16 studies for an effect size of 0.24. Only 3 patient characteristics were found to have sufficient power and to significantly moderate treatment outcomes. Cognitive-behavioral therapy was found to be more effective than other therapies in older adults ($g = 0.29$), in patients with comorbid addictive disorders ($g = 0.31$), and in university students ($g = 0.46$). Risk of bias was considerable in most of the included studies. It was estimated that it will take another 326 years to have sufficient statistical power for showing an effect size of $g = 0.50$ of the 27 characteristics, and 1,372 years to show an effect size of 0.24. Although several dozens of studies have compared the effects of psychotherapies in specific target groups, we will need to develop more powerful alternatives to comparative outcome studies in order to identify personalized treatments for depression.

Keywords: personalized medicine; depression; psychotherapy; meta-analysis; cognitive-behavioral therapy

Address correspondence to Pim Cuijpers, Ph.D., Department of Clinical Psychology, VU University Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands; e-mail: p.cuijpers@vu.nl.

Several early papers in *Behavior Therapy* have focused on the issue of personalizing psychological treatments for mental health problems. Brownell and Wadden (1991) proposed a three-stage model for identifying the best treatment for an individual with obesity and Sobell and Sobell (1973) developed a personalized treatment for people with alcohol-related problems in the context of a randomized trial. Although it has been recognized in the psychotherapy field for a long time that outcome research should not only focus on the effects of treatments, but

also on "which treatment, by whom, is most effective for this individual with that specific problem and under which set of circumstances" (Paul, 1967), personalized treatments have recently received much interest from researchers in health care in general (Katsanis, Javitt, & Hudson, 2008; Topol & Lauer, 2003). From that perspective, both articles in *Behavior Therapy* were far ahead of their time and provide perspectives on personalized treatments that are still highly relevant. In this paper, we build on these early studies and focus on the development of personalized treatments of depression using meta-analytic techniques.

It is well established that psychotherapies are effective in the treatment of depression, including cognitive-behavioral therapy (CBT; Churchill et al., 2001; Cuijpers et al., 2013), interpersonal psychotherapy (IPT; Cuijpers et al., 2011), problem-solving therapy (PST; Cuijpers, van Straten, & Warmerdam, 2007; Malouff, Thorsteinsson, & Schutte, 2007), behavioral activation (Ekers et al., 2014), and most likely psychodynamic therapies (Driessen et al., 2010; Leichsenring & Rabung, 2008). Although this has not been confirmed in all studies (Tolin, 2010), several dozens of trials directly comparing different types of psychotherapy have also shown that there are no or only minor differences in effects among these therapies and that all bona fide therapies seem to be equally effective or about equally effective in the treatment of depression (Barth et al., 2013; Cuijpers, 2014; Cuijpers, van Straten, Andersson, & van Oppen, 2008).

Although these therapies are effective in the treatment of depression, there is also much room for improvement. Modeling studies have shown that treatments for depression can reduce the disease burden of depression by only about 33% (Andrews, Issakidis, Sanderson, Corry, & Lapsley, 2004). More than 40% of the patients do not or only partially respond to treatment and less than one third of all patients are completely recovered after treatment (Hollon et al., 2002). Relapse rates are estimated to be 54% after 2 years and up to 85% within 15 years after recovery from an initial episode (Vittengl, Clark, Dunn, & Jarrett, 2007). Therefore, it is very important to improve the outcomes of treatment.

Personalized treatments are considered by many to be one of the major ways to improve outcomes of treatments in health care in general (Katsanis et al., 2008; Topol & Lauer, 2003), including mental health care (Cuijpers, Reynolds, Donker, Andersson, & Beekman, 2012; Schneider, Arch, & Wolitzky-Taylor, 2015; Simon & Perlis, 2010). "Personalized medicine" aims at identifying which characteristics of an individual predict the outcome of a specific treatment in order to get a better match between the individual and the treatment received (Cuijpers, 2014; Cuijpers et al., 2012; Simon & Perlis, 2010). These characteristics may include sociodemographic characteristics, patient preferences, and clinical characteristics of the depressive disorder, as well as biological markers. In the treatment of depression, personalized treatments are especially important because at this moment there is very little evidence that, on average, one treatment of depression is more effective than other treatments (Cuijpers, 2014).

In recent years, several approaches have attempted to develop personalized treatments in the field of mental health. Studies in the fields of pharmacogenetics, genomics, proteomics, metabolomics, neuroimaging, and neuroendocrinology have not yet led to effective personalized treatments (Cuijpers, 2014), but it could be that combining these techniques may lead in the longer term to successful therapies. New data mining techniques are now emerging that may also constitute a new approach to personalized treatments, and clinical staging has also been proposed as a model for personalized treatments of depression (Jain, Hunter, Brooks, & Leuchter, 2013; Rabinoff, Kitchen, Cook, & Leuchter, 2011; Riedel et al., 2011).

In order to provide personalized treatments for depression, we must identify characteristics of individuals that reliably predict differences in benefits and/or adverse effects of alternative depression treatments (Simon & Perlis, 2010). Two study designs examining specific patient characteristics could produce the evidence needed to personalize treatment selection (Simon & Perlis, 2010). In the first design, two treatments are compared in an unselected group of participants, and the researchers examine whether a specific characteristic of the participants moderates the relationship between treatment type and outcome (Kraemer, Wilson, Fairburn, & Agras, 2002). For example, in the NIMH Treatment of Depression Collaborative Research Program it was found that severity of depression at baseline significantly predicted differential treatment effects (Elkin et al., 1995). Pharmacotherapy appeared to be more effective than psychotherapy in the more severely depressed patients, while there was no difference between pharmacotherapy and psychotherapies in the less severely depressed. The disadvantage of these studies is that they were not designed to examine moderators and usually did not have enough statistical power to identify them (Brookes et al., 2004). If significant moderators are identified in such trials, this therefore always has to be confirmed in new randomized trials in which patients with this characteristic are randomized to the alternative therapies.

In the second type of research a group of patients with a specific characteristic is selected, and they are randomized to alternative treatments. For example, in a study of patients with multiple sclerosis it was found that CBT was more effective than supportive-expressive group therapy (Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001). In the current paper, we present the results of a systematic review of trials of this second type of trials, in which depressed patients with a specific characteristic are randomized to alternative psychological treatments in order to investigate if they respond differentially to different psychotherapies.

It is important to note that if a study does not include a direct comparison of alternative treatments, it is not possible to identify moderators or predictors of differential treatment response (Simon & Perlis, 2010). So, only studies in which two or more treatments are directly compared with each other can be used to examine moderators of treatments and will be included in the current systematic review.

Method

IDENTIFICATION AND SELECTION OF STUDIES

A database of 1,756 papers on the psychological treatment of depression was used. This database has been described in detail elsewhere (Cuijpers, van Straten, Warmerdam, & Andersson, 2008), and has been used in a series of earlier published meta-analyses (www.evidencebasedpsychotherapies.org). The database is continuously updated and was developed through a comprehensive literature search (from January 1966 to January 2015) in which 16,365 abstracts in PubMed (4,007 abstracts), PsycINFO (3,147), Embase (5,912), and the Cochrane Central Register of Controlled Trials (3,995) were examined. These abstracts were identified by combining terms indicative of psychological treatment and depression (both medical subject heading terms and text words). For this database, the primary studies from earlier meta-analyses of psychological treatment for depression were also checked to ensure that no published studies had been missed.

We included randomized trials on short-term or acute treatment of depression in which the effects of two types of the psychotherapy were directly compared with each other. From these trials we selected those that were aimed at a specific target group, meaning not an unselected group of adults with depression. We tried to be as broad as possible to define specific target groups, because any characteristic that predicts a better outcome is relevant for personalized treatments. There were no specific theoretically based or empirically derived reasons to select these target groups, but we selected these characteristics because there were enough clinical trials available examining them. In the selection of target groups, we built on previous meta-analyses of the literature in which we explored relevant subgroups of studies (Barth et al., 2013; Cuijpers, Van Straten, Warmerdam, & Smits, 2008). These specific target groups can be defined according to a predefined sociodemographic characteristic (such as older adults or minority groups), specific types of depression (such as dysthymia, chronic depression, or postnatal depression), and comorbid (mental or somatic) conditions.

We included studies in which one of six types of psychotherapy for adult depression were compared with another psychotherapy: (a) CBT (a therapy in which the therapist focuses on the impact that a patient's present dysfunctional thoughts affect current behavior and functioning), (b) PST (a psychological intervention that included at least the following elements: definition of personal problems, generation of multiple solutions to each problem, selection of the best solution, the working out of a systematic plan for this solution, and evaluation as to whether the solution has resolved the problem), (c) nondirective supportive counseling (NDST; any unstructured therapy without specific psychological techniques other than those common to all approaches, such as helping people to ventilate their experiences and emotions, and offering empathy), (d) IPT (highly structured manual-based psychotherapy that addresses interpersonal issues in depression to the exclusion of all other foci of clinical attention), (e) behavioral activation therapy without cognitive restructuring (an intervention to be an activity scheduled when the registration of pleasant activities and the increase of positive interactions between a person and his or her environment were the core elements of the treatment), and (f) psychodynamic therapy (a therapy with the primary objective of enhancing the patient's understanding, awareness, and insight about repetitive intrapsychic and intrapersonal conflicts). Extended definitions of each of these therapies are given in another paper (Cuijpers, van Straten, Andersson, et al., 2008). We selected these types of therapy because we knew from previous meta-analytic research that these are the most examined types of psychotherapy in depression (Cuijpers, van Straten, Andersson, et al., 2008). We excluded trials in which two therapies of the same type were compared with each other (e.g., when these therapies were offered in two different formats, like individual vs. telephone-administered therapy, or when a therapy was compared with the same therapy while one component was added or removed).

The other psychotherapy (that was compared with one of these six major categories of therapy)

did not necessarily have to belong to one of these categories as well. We included studies in which depression was defined according to a diagnostic interview in which a depressive disorder was established, but we also included studies in which participants had to score above a cutoff on a self-rating depression scale for inclusion in the study. We excluded studies on inpatients and on children and adolescents below 18 years of age. Only studies in English, German, Spanish, and Dutch were included.

RISK OF BIAS ASSESSMENT

We assessed the risk of bias of the studies according to four basic criteria suggested by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011): adequate sequence generation (the randomization scheme was generated correctly, like with a random numbers table or a computerized random number generator); allocation to conditions by an independent (third) party who was not involved in the trial; blinding of assessors of outcomes; and completeness of follow-up data (all randomized participants were included in the analyses). Data extraction was conducted by two independent researchers.

META-ANALYSES

We conducted separate analyses for each of the six types of psychotherapy. For each comparison we calculated the effect size indicating the difference between the two treatments at posttest, adjusted for small sample bias (Hedges's *g*; Hedges & Olkin, 1985). Effect sizes were calculated by subtracting (at posttest) the average score of the first treatment from the average score of the second treatment, and dividing the result by the pooled standard deviations of the two groups. We used only those instruments that explicitly measured symptoms of depression, such as the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) or the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). If more than one depression measure was used, the mean of the effect sizes was calculated (according to the methods described in Borenstein, Hedges, Higgins, & Rothstein [2009]; assuming a correlation of $r = 1$), so that each study provided only one effect size.

For each of the six types of psychotherapy, we calculated effect sizes for each study in which a specific target group was examined. We used the computer program Comprehensive Meta-Analysis (version 2.2.021) to calculate pooled mean effect sizes. As we expected considerable heterogeneity, we decided to calculate mean effect sizes using a random effects model. In all analyses we calculated the I^2 statistic as an indicator of heterogeneity in percentages (25% indicates low, 50% moderate, and 75% high heterogeneity; Higgins, Thompson, Deeks, & Altman, 2003). We calculated 95% confidence intervals (CI) around I^2 (Ioannidis, Patsopoulos, & Evangelou, 2007), using the noncentral chi–squared-based approach within the heterogi module for Stata (Orsini, Bottai, Higgins, & Buchan, 2006).

POWER CALCULATIONS

Because we examined six types of psychotherapy, and wanted to examine separate effect sizes for specific target groups (with a specific sociodemographic characteristic, type of depression, comorbid disorder, setting), we expected that for most comparisons insufficient statistical power was available to find clinically relevant effect sizes. Therefore, we conducted a power calculation for each comparison we examined.

For each comparison, we calculated how many studies are needed to have sufficient statistical power for finding an effect size of $g = 0.50$. Effect sizes of 0.50 and above have been defined as a threshold for clinical significance in several studies (Fournier et al., 2010; Kirsch et al., 2008; National Institute for Health and Clinical Excellence, 2009).

Because the threshold of $g = 0.50$ for clinical relevance has been criticized (Cuijpers, Turner, Koole, van Dijke, & Smit, 2014; Moncrieff & Kirsch, 2015), we also calculated the number of studies that are needed to calculate a more conservative estimate of a clinically relevant effect size based on the "minimally important difference." This has been estimated to be $g = 0.24$ (Cuijpers et al., 2014).

For each comparison, we calculated the mean number of participants in each treatment condition. Then we calculated how many studies with this number of participants would be needed to find an effect size of $g = 0.50$ or $g = 0.24$. The power calculations were conducted according to the procedures suggested by Borenstein et al. (2009). In these calculations we conservatively assumed a medium level of between-study variance ($\tau^2 = 0.67$); a statistical power of 0.80; and a significance level, alpha, of .05.

Because we calculated the number of studies needed to show significant effect sizes of 0.50 and 0.24, we were also able to calculate what percentage of the studies would be needed to find that these effect sizes have actually been conducted. This gives an indication of how many studies still have to be conducted in order to find significant effect sizes of $g = 0.50$ and $g = 0.24$ for each of the examined characteristics.

Results

SELECTION AND INCLUSION OF STUDIES

After examining a total of 16,365 abstracts (12,196 after removal of duplicates), we retrieved 1,756 full-text papers for further consideration. We excluded 1,715 of the retrieved papers. The reasons for excluding studies are given in Figure 1. Forty-one studies met inclusion criteria. Figure 1 presents a flowchart describing the inclusion process.

CHARACTERISTICS OF INCLUDED STUDIES

Selected characteristics of the included studies are presented in Table 1. In the 41 included studies, a total of 2,741 patients participated (978 in the NDST, 812 in CBT, 226 in PST, 221 in behavioral activation therapy, 91 in IPT, 70 in psychodynamic therapy, and 343 in other therapies). In the 41 studies a total of 91 psychotherapy conditions were included (27 NDST, 25 CBT, 9 behavioral activation, 8 PST, 5 IPT, 5 psychodynamic therapy, and 12 other therapies). The average number of patients per condition was 30. A total of 27 specific target groups were included in the studies (Table 1).

RISK OF BIAS

The risk of bias in most of the studies was considerable. Twelve of the 41 studies reported an adequate sequence generation (29%), while the other 29 did not report a sequence generation method. Eight studies reported allocation to conditions by an independent (third) party (20%). Twenty studies reported using blinded outcome assessors (49%), and 7 used only self-report outcomes, the others did not report blinding of assessors. In 17 studies intent-to-treat analyses (completeness of follow-up data) were conducted (41%). Only 2 studies (5%) met all

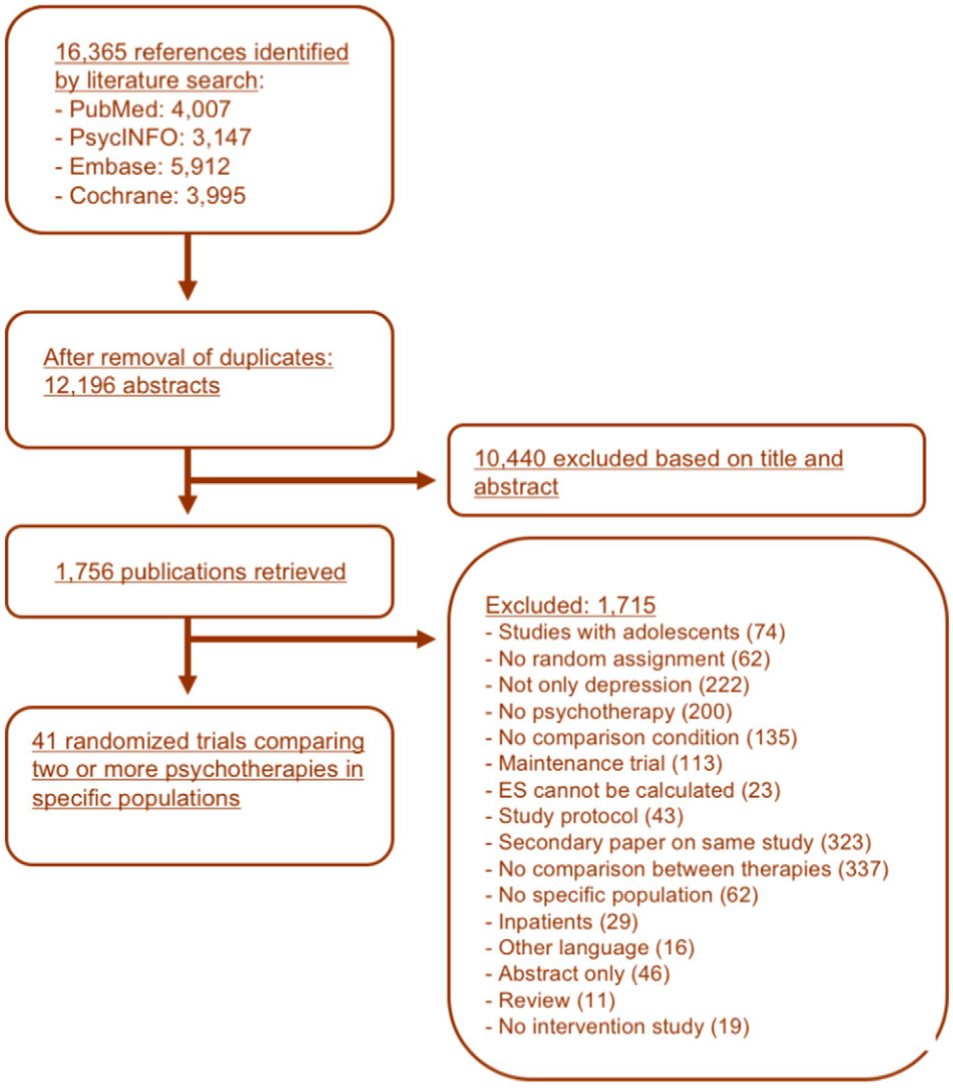

FIGURE 1 Flowchart of inclusion of studies.

Table 1
Selected Characteristics of Studies Comparating Different Types of Psychotherapy for Depression in Specific Target Populations

	Target group	Recr	Depression	Conditions	*N*	Nsess	Form	Risk of bias[a]	C
Alexopoulos, 2003	Older adults with executive dysfunction	Clin	MDD	1. PST 2. SUP	12 12	12	Ind	– – + +	US
Arean, 2010	Older adults with executive dysfunction	Comm	MDD	1. PST 2. SUP	90 97	12	Ind	– – + +	US
Arean, 1993	Older adults	Comm	MDD	1. PST 2. Reminiscence	19 28	12	Grp	– – + –	US
Ashman, 2014	Traumatic brain injury	Comm	SR	1. CBT 2. SUP	39 38	16	Ind	+ + – –	US
Ayen, 2004	Women in menopause	Comm	Mood	1. CBT 2. SUP	11 20	12	Grp	– – – –	EU
Beutler, 2003	Stimulant dependent	Comm	Mood	1. CBT 2. Narrative ther 3. Prescr. ther	13 11 12	20	Ind	– – – –	US
Choi, 2014	Low-income homebound older adults			1. PST tel 2. PST ind 3. SUP	38 35 34	6	Tel Ind	– – – +	US
Evans, 1995	Cancer patients	Other	SR	1. CBT 2. SUP	27 21	8	Grp	– – sr –	US
Gallagher, 1982	Older adults	Comm	MDD	1. CBT 2. BAT 3. DYN	10 10 10	16	Ind	– – – –	US
Gallagher, 1981	Older adults	Clin	SR	1. BAT 2. SUP	12 11	10	Grp	– – sr –	US
Gallagher, 1994	Family caregivers	Clin	Mood	1. CBT 2. DYN	31 21	20	Ind	+ – – –	US
Hautzinger, 2008	Older adults	Comm	SR	1. CBT 2. SUP	50 51	15	Ind	– – + +	EU
Hayden, 2012	Diabetes in pregnancy	Other	MDD	1. CBT 2. SUP	20 14	12	Ind	+ – + –	US
Heckman, 2011	HIV patients	Comm	SR	1. Support 2. Coping	105 104	12	Grp	+ – sr +	US
Hogg, 1988	Students	Clin	SR	1. CBT 2. Interp grp ther	13 14	8	Grp	– – sr –	US
Hopko, 2011	Breast cancer patients	Other	MDD	1. BAT 2. PST	42 38	8	Ind	+ – – +	US
Kay-Lambkin, 2011	Addictive disorders	Comm	SR	1. CBT+MI 2. cCBT/MI 3. SUP	88 97 89	10	Ind Gsh Ind	– + + +	AU
Kelly, 1993	HIV patients	Comm	SR	1. CBT 2. SUP	27 14	8	Grp	– – sr –	US
Kiosses, 2010	Cognitively impaired disabled elders	Comm	MDD	1. PST 2. SUP	13 12	12	Ind	– – + +	US
Koszycki, 2012	Infertile women	Comm	MDD	1. IPT 2. SUP	15 16	12	Ind	– – – +	CA
Maina, 2005	Minor depression	Clin	Mood	1. DYN 2. SUP	10 10	20	Ind	– – + +	EU
Manicavasgar, 2010	Nonmelancholic depression	Comm	MDD	1. CBT 2. MBCT	26 19	6	Grp	– – – –	AU
Markowitz, 1998	HIV patients	Comm	SR	1. IPT 2. CBT 3. SUP	24 27 24	16	Ind	+ + + +	US
Markowitz, 2005	Dysthymia	Comm	Mood	1. IPT 2. SUP	23 26	17	Ind	+ – + +	US
Markowitz, 2008	Dysthymia and alcohol problems	Comm	Mood	1. IPT 2. SUP	14 12	17	Ind	+ – + +	US

(continued on next page)

Table 1 (*continued*)

	Target group	Recr	Depression	Conditions	*N*	Nsess	Form	Risk of bias[a]	C
Milgrom, 2005	PPD	Other	Mood	1. CBT	46	9	Grp	+ + + +	US
				2. SUP grp	47		Grp		
				3. SUP ind	66		Ind		
Mohr, 2001	MS patients	Other	MDD	1. CBT	20	16	Ind	– – – +	US
				2. SUP	19		Grp		
Mohr, 2005	MS patients	Other	SR	1. CBT	60	16	Tel	– – + +	US
				2. SUP	62				
Mondin, 2014	Young adults	Comm	Mood	1. CBT	60	7	Ind	– + + –	Bra
				2. Cogn narr ther	60				
Padfield, 1976	Rural women of low socioeconomic status	Comm	Mood	1. SUP	12	12	Ind	– – – –	US
				2. BAT	12				
Pellowe, 2007	Students	Comm	SR	1. SUP	25	4	Grp	– – sr –	US
				2. ACT	27				
Rovner, 2014	Age-related macular degeneration	Other	Mood	1. BA	96	6	Ind	+ + + –	US
				2. SUP	92				
Schramm, 2010	Early-onset chronic depression	Clin	Mood	1. IPT	15	22	Ind	+ + + –	EU
				2. CBASP	14				
Shaw, 1977	Students	Comm	SR	1. CBT	8	8	Grp	– – + –	US
				2. BAT	8				
				3. SUP	8				
Taylor, 1977	Students	Comm	SR	1. CBT	7	6	Ind	– – sr +	CA
				2. BAT	7				
Teri, 1997	Dementia patients	Other	Mood	1. BAT	23	9	Ind	– – + –	US
				2. PST	19				
Thompson, 1987	Older adults	Comm	MDD	1. CBT	21	18	Ind	– – – –	US
				2. BAT	17				
				3. DYN	20				
Thompson, 1984	Older adults	Other	MDD	1. CBT	14	18	Ind	– – – –	US
				2. BAT	6				
				3. DYN	9				
Tovote, 2014	Patients with diabetes	Other	SR	1. CBT	32	8	Ind	+ – – +	EU
				2. MBCT	31				
Verduyn, 2003	Mothers of young children	Other	SR	1. CBT	30	16	Grp	– + + –	EU
				2. SUP	28				
Zettle, 1989	Women	Comm	SR	1. CBT	10	12	Grp	– – + –	US
				2. Distancing	11				

Note. References of the included studies are listed in the Appendix.
AU = Australia; BAT = behavioral activation therapy; Bra = Brazil; C = country; CA = Canada; CBASP = cognitive-behavioral analysis system of psychotherapy; CBT = cognitive-behavioral therapy; cCBT = computerized cognitive-behavioral therapy; Clin = recruitment from clinical samples; Cogn = cognitive; Comm = recruitment from community samples; DYN = psychodynamic therapy; EU = Europe; Form = format; Grp = group; Ind = individual; Interp = interpersonal; IPT = interpersonal psychotherapy; MBCT = mindfulness-based cognitive therapy; MDD = major depression; MI = motivational interviewing; Mood = mood disorder; MS = multiple sclerosis; Narr = narrative; Nsess = number of sessions; PPD = postpartum depression; Prescr = prescriptive; PST = problem-solving therapy; Recr = recruitment; SR = self-report; SUP = nondirective supportive counseling; Tel = telephone; Ther = therapy; US = United States.
[a] In this column a positive (+) or negative (–) sign is given for four quality criteria, respectively: allocation sequence, concealment of allocation to conditions, blinding of assessors, and intention-to-treat analyses. Sr indicates that only self-report measures were used.

quality criteria. Seven studies (17%) met three or four of the criteria and are considered in the rest of this paper as having low risk of bias.

CBT versus other psychotherapies

We identified 16 patient characteristics that were examined in comparative outcome studies of CBT versus other psychotherapies (Table 2). We found that CBT was significantly more effective than other therapies in older adults (>55 years, g = 0.29), university students (g = 0.51), when patients also had an addiction problem (g = 0.31), in multiple sclerosis patients (g = 0.42), in women in their menopause (g = 1.56), and in young adults (18–29 years, g = 0.59). As sensitivity analyses we limited the analyses to studies with low risk of bias. We found that none of the characteristics remained significant (Table 3). In another series of sensitivity analyses we limited the analyses to those characteristics with four or more comparisons (and therefore having

Table 2
Comparative Studies of Psychotherapies for Specific Target Populations: Hedges's g[a]

		N_{comp}	g	95% CI	I^2	
CBT versus other therapies						
Type of depression	• Postpartum depression	2	-0.16	-0.46 ~ 0.15	0	-
	• Nonmelancholic	1	-0.15	-0.73 ~ 0.43	0	
Sociodemographic	• Older adults	7	0.29	0.01 ~ 0.56	0	0 ~ 58
	• Women	1	-0.43	-1.26 ~ 0.40	0	
	• Women in menopause	1	1.56	0.74 ~ 2.37	0	
	• Young adults	1	0.59	0.10 ~ 1.08	0	
Comorbid conditions	• Addictive problems	4	0.31	0.01 ~ 0.62	0	0 ~ 68
	• HIV	3	-0.33	-0.66 ~ 0.00	0	-
	• MS patients	2	0.42	0.11 ~ 0.73	0	
	• Cancer	1	-0.16	-0.72 ~ 0.40	0	-
	• Diabetes in pregnancy	1	0.41	-0.26 ~ 1.09	0	-
	• Diabetes	1	0	-0.49 ~ 0.49	0	-
	• Traumatic brain injury	1	0.04	-0.51 ~ 0.60	0	
Other	• Students	5	0.46	0.05 ~ 0.88	23	0 ~ 76
	• Mothers of young children	1	0.06	-0.44 ~ 0.57	0	-
	• Family caregivers	1	0.41	-0.60 ~ 1.42	0	-
Nondirective counseling versus other therapies						
Type of depression	• Dysthymia	1	-0.05	-0.60 ~ 0.50	0	-
	• Dysth + alcohol problems	1	-0.62	-1.40 ~ 0.15	0	-
	• Minor depression	1	-0.03	-0.87 ~ 0.81	0	-
	• Nonmelancholic depression	1	-0.15	-0.73 ~ 0.43	0	-
Sociodemographic	• Low-inc homeb. elderly	2	-0.68	-1.02 ~ -0.34	0	-
	• Mothers of young children	1	-0.06	-0.57 ~ 0.44	0	-
	• Older adults	1	-0.45	-0.99 ~ 0.09	0	-
	• Rural women of low SES	1	-0.69	-1.49 ~ 0.11	0	-
Comorbid conditions	• Addictive disorders	2	-0.27	-0.62 ~ 0.08	0	-
	• Cancer patients	1	0.16	-0.40 ~ 0.72	0	-
	• Cogn. imp. disabled elders	1	-0.75	-1.54 ~ 0.04	0	-
	• Diabetes in pregnancy	1	-0.41	-1.09 ~ 0.26	0	-
	• HIV patients	5	-0.02	-0.22 ~ 0.18	33	0 ~ 75
	• Age-rel. macular degen.	1	-0.35	-0.79 ~ 0.10	0	-
	• Traumatic brain injury	1	-0.04	-0.60 ~ 0.51	0	-
Other	• Infertile women	1	-0.61	-1.31 ~ 0.09	0	-
	• Students	3	-0.78	-1.21 ~ -0.34	0	0 ~ 73
	• Women in menopause	1	-1.56	-2.37 ~ -0.74	0	-
PST versus other therapies						
Sociodemographic	• Older adults with exec. dysf.	3	0.49	0.24 ~ 0.75	28	0 ~ 80
	• Low-income homeb. elderly	2	0.68	0.34 ~ 1.02	0	-
	• Older adults	1	0.52	-0.07 ~ 1.11	0	-
Comorbid conditions	• Dementia patients	1	-0.37	-0.98 ~ 0.23	0	-
	• Breast cancer patients	1	-0.01	-0.44 ~ 0.43	0	-
IPT versus other therapies						
	• Dysthymia	1	0.05	-0.50 ~ 0.60	0	-
	• Dyst. + alcohol problems	1	0.62	-0.15 ~ 1.40	0	-
	• HIV patients	2	0.51	0.12 ~ 0.91	0	-
	• Infertile women	1	0.61	-0.09 ~ 1.31	0	-
Psychodynamic versus other therapies						
	• Older adults	4	-0.21	-0.57 ~ 0.15	0	-
	• Family caregivers	1	-0.41	-1.42 ~ 0.60	0	-
	• Minor depression	1	0.03	-0.81 ~ 0.87	0	-
Behavioral activation versus other therapies						
	• Older adults	6	0.07	-0.24 ~ 0.37	0	0 ~ 61
	• Students	2	-0.59	-1.29 ~ 0.11	35	-

(continued on next page)

Table 2 (*continued*)

	N_{comp}	*g*	95% CI	I^2	
Behavioral activation versus other therapies					
• Breast cancer patients	1	0.01	-0.43 ~ 0.44	0	-
• Dementia patients	1	0.00	-0.61 ~ 0.60	0	-
• Rural women of low SES	1	0.69	-0.11 ~ 1.49	0	-

Note. Underlined values for g are significantly different from zero. Age-rel = age-related; CBT = cognitive-behavioral therapy; CI = confidence interval; Cogn imp = cognitive impairment; Degen = degenerative; Dyst = dysthymia; Exec dysf = executive dysfunction; HIV = human immunodeficiency virus; Homeb = homebound; IPT = interpersonal therapy; Low inc = low income; MS = multiple sclerosis; N_{comp} = number of comparisons; PST = problem-solving therapy; SES = socioeconomic status.

[a] According to the random effects model.

sufficient power for finding an effect size of *g* = 0.50, see below). We have reported the alternative psychotherapy against which CBT was compared in Table 4. As can be seen in these comparisons only the CBT versus behavioral activation therapy in university students remained significant (*g* = 0.71 in favor of CBT).

The average number of patients per condition was 30, and our power calculations indicated that we would need 4 studies per characteristic to find an effect size of *g* = 0.50 (a total of 64 studies for the 16 characteristics) and 16 studies per characteristic to find an effect size of *g* = 0.24 (256 studies for the 16 characteristics). Overall, we had 34 comparisons (53% of the studies needed to show an effect size of *g* = 0.50, and 13% of the studies when we used *g* = 0.24). Only 7 comparisons had a low risk of bias, which was 11% of the studies needed to show an effect of *g* = 0.50, and 3% for an effect size of *g* = 0.24.

Table 3
Comparative Studies of Psychotherapies for Specific Target Populations With Low Risk of Bias: Hedges's *g*[a,b]

	N_{comp}	*g*	95% CI	I^2
CBT versus other therapies				
• Addictive disorders	2	0.27	-0.08 ~ 0.62	0
• HIV patients	2	-0.31	-0.70 ~ 0.08	29
• PPD	2	-0.16	-0.46 ~ 0.15	0
• Traumatic brain injury	1	0.04	-0.51 ~ 0.60	0
Nondirective counseling versus other therapies				
• HIV patients	3	-0.12	-0.34 ~ 0.11	5[c]
• Addictive disorders	2	-0.27	-0.62 ~ 0.08	0
• Age-rel macul degeneration	1	-0.35	-0.79 ~ 0.10	0
• Dysthymia	1	-0.05	-0.60 ~ 0.50	0
• Dysthymia + alc. problems	1	-0.62	-1.40 ~ 0.15	0
• Traumatic brain injury	1	-0.04	-0.60 ~ 0.51	0
IPT versus other therapies				
• Dysthymia	1	0.05	-0.50 ~ 0.60	0
• Dysthymia + alc. problems	1	0.62	-0.15 ~ 1.40	0
• HIV patients	2	0.51	0.12 ~ 0.91	0

Note. Age-rel = age-related; Alc = alcohol; CBT = cognitive-behavioral therapy; CI = confidence interval; HIV = human immunodeficiency virus; IPT = interpersonal therapy; Macul = macular; N_{comp} = number of comparisons; PPD = postpartum depression.

[a] According to the random effects model.

[b] No studies on problem-solving, behavioral activation, and psychodynamic therapies had low risk of bias

[c] The 95% CI of this value for I^2 is 0 ~ 74. For the other values of I^2 in this table the 95% CI cannot be calculated because the number of studies was too small.

NDST VERSUS OTHER PSYCHOTHERAPIES

NDST was examined in 17 specific target populations (Table 3). NDST was significantly less effective than other therapies in low-income homebound elderly (*g* = –0.68), in students (*g* = –0.78), and in menopausal women (*g* = –1.56). When we looked only at the studies with low risk of bias, none of the outcomes was significant.

For the 17 characteristics examined in these studies, 72 comparisons are needed to find an effect size of *g* = 0.50, (4 per characteristic) and 272 studies to find an effect size of *g* = 0.24. The 26 comparisons we had was 36% of the studies needed to show an effect size of *g* = 0.50 and 10% of the studies for showing *g* = 0.24. Only 9 comparisons had a low risk of bias (13% of the studies needed to show an effect of *g* = 0.50 and 3% for an effect size of *g* = 0.24).

PROBLEM-SOLVING, INTERPERSONAL, PSYCHODYNAMIC, AND BEHAVIORAL ACTIVATION THERAPY VERSUS OTHER THERAPIES

Problem-solving, interpersonal, psychodynamic, and behavioral activation therapy were examined in eight, four, three, and six specific target groups, respectively (Table 2). We found that PST was more effective than other therapies in older adults with executive dysfunctions (*g* = 0.49) and in low-income homebound elderly (*g* = 0.68), and IPT was more effective than other therapies in HIV patients (*g* = 0.51).

When we looked only at the four studies with low risk of bias examining IPT, none of the outcomes for specific target groups remained statistically significant. No studies on PST, behavioral activation therapy, and psychodynamic therapies had low risk of bias.

Table 4
Comparative Outcome Studies for Adult Depression in Specific Target Groups With More Than Four Comparisons[a]

		N_{comp}	g	95% CI	I^2	95% CI	P[b]
CBT versus other therapies							
Older adults	• Behavioral activation	2	0.07	-0.45 ~ 0.58	0	[c]	0.73
	• Psychodynamic therapy	3	0.38	-0.07 ~ 0.83	0	0 ~ 73	
	• NDST	1	0.45	-0.10 ~ 1.00	0	[c]	
	• Other therapy	1	0.18	-0.66 ~ 1.02	0	[c]	
Students	• Behavioral activation	3	0.71	0.13 ~ 1.30	2	0 ~ 73	0.12
	• NDST	1	0.90	-0.09 ~ 1.88	1	[c]	
	• Other therapy	1	-0.17	-0.92 ~ 0.57	1	[c]	
Addictive disorders	• NDST	2	0.27	-0.08 ~ 0.62	0	[c]	0.63
	• Other therapy	2	0.45	-0.19 ~ 1.09	0	[c]	

Note. CBT = cognitive-behavioral therapy; CI = confidence interval; N_{comp} = number of comparisons; NDST = nondirective supportive therapy.
[a] According to the random effects model.
[b] The p values in this column indicate whether the difference between the effect sizes in the subgroups is significant.
[c] Confidence intervals around I^2 cannot be calculated if there are fewer than three groups.

The five characteristics examined for PST were examined in eight studies (40% of the studies needed to show an effect size of g = 0.50 and 10% of the studies needed to show an effect size of g = 0.24). The four characteristics for IPT were examined in six studies (38% of the studies needed to find g = 0.50 and 9% of the studies needed to find g = 0.24). The three characteristics examined for psychodynamic therapy were examined in six studies (50% of the studies needed to show g = 0.50 and 13% of the studies to show g = 0.24). Finally, behavioral activation therapy was examined in 11 studies of five specific target groups (55% of the studies needed to show an effect size of g = 0.50 and 14% of the studies needed to show g = 0.24).

OVERALL OUTCOMES

When we limit the outcomes to the comparisons with sufficient power to find an effect size of g = 0.50 (number of studies > 4) and which were significant, only three specific target groups remained. CBT was more effective than other psychotherapies in older adults, in patients with comorbid alcohol problems, and in university students. Several of the studies on which these outcomes were based had a high risk of bias, so these results should also be considered with caution.

The 41 studies examined a total of 27 characteristics. In order to examine whether these six types of psychotherapy were more effective than other therapies we would need a total of 648 studies to find an effect size of g = 0.50, and 2,592 studies to find an effect size of g = 0.24. The 41 studies that have been conducted to examine these specific target groups are 6% of the studies needed to find an effect size of g = 0.50 and 2% of the studies needed to find an effect size of g = 0.24. Only 7 studies had low risk of bias, which is 1% of the studies needed to show an effect size of g = 0.05, and 0.2% of the studies needed to show an effect size of g = 0.24. The number of studies needed would increase exponentially if we would examine the contrast between each of the specific therapies, so not CBT versus all psychotherapies, but only CBT versus IPT, CBT versus PST, and so on.

Since the year 2000, 26 studies were conducted (1.86 study per year). If the number of studies will be conducted at the same rate in the future, it will take 326 years before all of these 27 characteristics have been examined with sufficient power to find an effect size of g = 0.50 and 1,372 years for an effect size of g = 0.24, assuming that all new studies have a low risk of bias.

Discussion

If we want to build the development of personalized treatments on the gold standard of evidence-based health care, the randomized trial, it is important to examine whether one treatment is more effective than another treatment in a specific subgroup of patients. We conducted a systematic review and meta-analysis of randomized trials comparing two psychotherapies directly in subgroups of depressed adults. We focused on the six best examined types of psychotherapy for adult depression. We found that 27 characteristics of patients had been examined in 41 trials. However, only for a few characteristics was sufficient statistical power available to show a clinically relevant effect size (of g = 0.50). CBT was found to be more effective than other therapies in older adults (g = 0.29), in patients with comorbid addictive disorders (g = 0.31), and in university students (g = 0.46). For none of the other therapies did we find

characteristics that had sufficient statistical power to show that one therapy was more effective than another therapy. When we used a more conservative estimate of clinical relevance, there was not sufficient power for any of the 27 characteristics.

From a clinical point of view it is worth noting that CBT stands out as being superior in at least three samples (older adults, patients with comorbid addictive disorders, and university students). Even if we would need larger studies and more characteristics to conclude that CBT is more effective than other psychotherapies overall, and this finding would contrast with most (e.g., Cuijpers et al., 2013; Marcus, O'Connell, Norris, & Sawaqdeh, 2014; Wampold, Minami, Baskin, & Callen Tierney, 2002), but not all (Tolin, 2010), previous meta-analytic findings in the depression literature, it is still possible that CBT is slightly more effective in certain subgroups.

A disturbing finding was that only 7 of the 41 studies had low risk of bias. That means that in the large majority of studies there is a considerable chance that the findings are biased. This is in line with earlier meta-analytic research showing that the risk of bias is high in studies on psychotherapies for adult depression (Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, 2010). It is important to note that in this earlier meta-analysis it was found that studies with high risk of bias had considerably higher effect sizes than studies with low risk of bias. This has probably influenced the outcomes of the current meta-analysis as well.

This meta-analysis also suggests that examining the comparative effects of different psychotherapies in specific target groups is probably not the most efficient way to develop personalized treatments. We calculated that if we continue to do randomized comparative outcome studies at the same rate as they have been done in recent years, it will take more than 300 years to examine the 27 characteristics in the 7 psychotherapies when a liberal threshold for clinical relevance is taken and more than 1,300 years when a more stringent threshold is used. Clearly this is not a feasible approach.

In recent years, several other techniques have been used to develop personalized treatments of mental health problems. In a more comprehensive review of these techniques (Cuijpers, 2014), we have described that some studies have used data-mining techniques in large samples of patients to develop decision trees for defining what the best treatment is for a specific patient (Jain et al., 2013; Rabinoff et al., 2011; Riedel et al., 2011). Clinical staging has also been proposed as a framework for developing personalized treatments for depression, but unfortunately there is very little evidence at this moment that clinical staging results in better outcomes (Cuijpers, 2014). Other methods have focused on integrating the results of different predictors of outcome into one estimate of the best treatment for a specific patient (DeRubeis et al., 2014; Kraemer, 2013). Although these approaches cannot be based on the scientific strength of the experimental design of randomized trials (like the trials included in this review), these approaches seem much more feasible than focusing on comparative outcome trials in specific patient subpopulations. And these studies can be used to generate prediction algorithms, which could then be tested in randomized trials.

It has also been suggested that if we want to develop personalized treatments for mental disorders, these analyses should be based on the individual, not the group (Molenaar, 2004; Molenaar & Campbell, 2009). Such methods hold promise and provide a completely new way of thinking about mental disorders and their treatment. They may provide a better way of developing personalized treatments than the approach described in this paper; however, randomized trials showing that these methods indeed result in better outcomes are still needed.

This systematic review has several strengths and limitations; some have been described already. The studies examined in this review are not the only type of studies that result in relevant information about specific treatments for specific target populations. However, the trials we reviewed do result in the best available evidence, as they are based on randomized trials and not on secondary post hoc analyses of earlier trials. Although the number of studies was relatively large, many more are needed before we actually are capable of personalizing treatments for adult depression, and it may take hundreds of years before a relatively small set of predictors have been examined with sufficient statistical power. A problem with the current set of studies was that the risk of bias in the included studies was considerable, and only a selected number of potentially relevant moderators were examined. It should also be stated as a limitation that the characteristics we selected in this study were not theoretically based or empirically derived, but were only selected because there were enough clinical trials available that examined them. Another problem with the current studies is that in most trials the standard manuals of the treatment were adapted for use with the specific target group in the study. When the effect sizes found in these studies are different from those found in generic trials, it is impossible to know whether these differences are caused by the adapted manuals or by the different characteristics of the target group. Furthermore, we only examined short-term outcomes, whereas

longer-term outcomes may be more relevant from a clinical point of view.

Personalized treatment of depression is one of the most important challenges for mental health researchers in the next decades. Although several dozens of comparative outcome studies in subpopulations have been conducted, this seems not the best way to develop personalized treatments for adult depression.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

Funding

No funding was received for this project.

Appendix A. References of the Included Studies

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Received: June 30, 2015
Accepted: April 26, 2016
Available online: 5 May 2016